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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,694	01/17/2006	Irina A Buhimschi	035394-0295	6784

22428 7590 07/12/2006

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EXAMINER	
LUM, LEON YUN BON	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,694	BUHIMSCHI ET AL.	
	Examiner	Art Unit	
	Leon Y. Lum	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/13/05, 3/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The use of the trademark names Ciphergen H4 and H50 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

2. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 90 requires a patient that does not have a white blood cell count that is elevated out of the normal range. However, there is no support for this limitation anywhere in the body of the specification.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 45-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. In claims 45 and 61, line 3 of both claims, the phrase "associated with" is vague and indefinite. The specification does not define the phrase and it is unclear how the "biomarker" (line 3) is associated with the "intra-amniotic inflammation" (line 3).

6. Claim 46 is vague and indefinite because it is unclear whether the claimed adsorbent includes the solid substrate or if the claimed adsorbent consists only of the antibody.

7. In claim 51, lines 1-2, the phrase "hydrophobic adsorbent" is vague and indefinite. It is unclear whether the claimed phrase refers to an adsorbent that is purely hydrophobic or an adsorbent that has hydrophobic portions. If the adsorbent is an antibody, for example as claimed in claim 46, does an antibody with both hydrophilic and hydrophobic epitopes qualify as a hydrophobic absorbent?

8. Claims 52 and 89 contain the trademark/trade names Ciphergen H4 and H50. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218

USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade names are used to identify/describe a biosensor substrate and, accordingly, the identification/description is indefinite.

9. In claims 77 and 82, line 1 of both claims, the term "qualifying" is vague and indefinite. The specification does not define the term and it is unclear what is being claimed. How the does instant term limit the phrase "the risk of preterm delivery" (line 1 of the claims)?

10. In claim 82 (line 5) and claim 83 (line 2), the phrase "is keyed to" is vague and indefinite. The specification does not define the phrase and it is unclear how this phrase limits the claimed "pattern-recognition analysis" that precedes the phrase in each claim.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 45-47, 59-60, 77, and 79 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hitomi et al (US 5,976,832).

Hitomi et al teach an assay that detects CAAF1 (i.e. calgranulin) in amniotic fluid on an ELISA plate for the diagnosis of inflammatory disease (i.e. mixing an adsorbent that binds to at least one biomarker associated with intra-amniotic inflammation with a sample of amniotic fluid and then monitoring said mixture for binding between said biomarker and said adsorbent, wherein said assay detects at least one biomarker that is a calgranulin; analyzing a sample of amniotic fluid from said subject for a level of at least one calgranulin; kit comprising at least one absorbent that detects a calgranulin). See column 21, line 55 to column 22, line 58, especially column 21, lines 56-66 and column 22, lines 52-58.

With regards to claims 46-47, Hitomi et al reference teaches coating of monoclonal antibodies in an ELISA plate (i.e. antibody immobilized on a solid substrate; ELISA). See column 21, lines 59-61.

With regards to claims 59 and 79, Hitomi et al reference teaches MRP8 as a member of the S100 protein family (i.e. calgranulin A). See column 1, lines 29-30.

With regards to claims 60 and 79, Hitomi et al reference teaches assay of CAAF1 (i.e. calgranulin C), as stated above. See column 21, line 57.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 48-51, 82, and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Krone et al (Analytical Biochemistry, 1997).

Hitomi et al reference has been disclosed above, but fails to teach that the solid substrate is a probe and said biomarker is detected by laser desorption/ionization mass spectrometry.

Krone et al reference teaches a BIAcore CM5 biosensor chip (i.e. probe) that is covalently derivatized with an antibody, and the step wherein species detected during surface plasmon resonance for biomolecular interaction analysis is interfaced with MALDI mass spectrometry (i.e. laser desorption/ionization mass spectrometry; pattern recognition analysis that is keyed to at least one peak), in order to perform ligand identification and quantitation, and allow for the rapid, sensitive, and accurate investigations of biomolecular interactions. See page 125, right column, 1st full paragraph to page 126, left column, 1st full paragraph; and page 131, right column, 1st full paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Hitomi et al with a BIAcore CM5 biosensor chip covalently derivatized with an antibody, and the step wherein species detected during surface plasmon resonance for biomolecular interaction analysis is interfaced with MALDI mass spectrometry, as taught by Krone et al, in order to perform ligand identification and quantitation, and allow for the rapid, sensitive, and accurate

investigations of biomolecular interactions. The benefits of quantifiable results, efficiency, and effectiveness provide the motivation to combine the BIAcore BM5 biosensor chip and the MALDI mass spectrometry of Krone et al in the method of Hitomi et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including a BIAcore CM5 biosensor chip and detection step using MALDI mass spectrometry, as taught by Krone et al, in the method of Hitomi et al, since Hitomi et al teach binding interactions between antigen and antibody, and the chip and detection method of Krone et al are used to detect antigen binding to immobilized antibody on a chip surface.

With regards to claim 51, Hitomi et al reference teaches anti-CAAF1 monoclonal antibody CAAF1-22-5 (i.e. hydrophobic adsorbent). See column 21, lines 57-58.

With regards to claim 84, Hitomi et al reference teaches MRP8 as a member of the S100 protein family (i.e. calgranulin A). See column 1, lines 29-30.

With regards to claim 84, Hitomi et al reference teaches assay of CAAF1 (i.e. calgranulin C), as stated above. See column 21, line 57.

17. Claims 52 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Krone et al (Analytical Biochemistry, 1997) as applied to claims 45 and 50-51 above, and further in view of Pham (US 2002/0060290).

Hitomi et al and Krone et al references have been disclosed above, but fail to teach that said probe is a Ciphergen H4 probe.

Pham reference teaches a hydrophobic H4 chip from Ciphergen Biosystems, Inc. in order to provide a substrate with a reverse phase adsorbent for hydrophobic interactions. See page 5, sections 0073-0079.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Hitomi et al and Krone et al with a hydrophobic H4 chip from Ciphergen Biosystems, Inc. as taught by Pham, in order to provide a substrate with a reverse phase adsorbent for hydrophobic interactions. The advantage of having a substrate specific for hydrophobic interactions provides the motivation to combine the hydrophobic H4 chip of Pam with the method of Hitomi et al and Krone et al. In addition, one of ordinary skill in the art at the time of the invention would have reasonable expectation of success in including a Ciphergen H4 probe, as taught by Pham, in the method of Hitomi et al and Krone et al, since Hitomi et al and Krone et al teach the method of detecting analytes with immobilized antibodies on a chip surface, and the Ciphergen H4 probe is one example of a chip with the capability to immobilize adsorbents on a surface to bind analytes.

18. Claims 53-56, 78, 80-81, 83, and 85-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Heine et al (US 6,174,664 B1).

Hitomi et al reference has been disclosed and additionally teaches an ELISA assay with wells for either a standard substance or specimens. See column 21, lines 62-67. However, Hitomi et al reference fails to teach that the assay additionally tests for

the presence of at least one defensin in said sample of amniotic fluid and that said defensin is HNP-1.

Heine et al teach an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, in order to provide an immunoassay to screen for intra-amniotic infection by detecting a type of neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. See column 1, lines 39-63; column 1, line 66 to column 2, line 9; column 4, lines 25-34; column 6, line 47 to column 7, line 52.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Hitomi et al an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, as taught Heine et al, in order to provide an immunoassay to screen for intra-amniotic infection by detecting a type of neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. The ability to detect an analyte that is stable and does not degrade provides the motivation to combine the detecting step of Heine et al with the method of Hitomi et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including testing for defensins HNP1-3, as taught by Heine et al, in the method of Hitomi et al and Vogl et al, since Hitomi et al teach ELISA assays, and the testing for HNP1-3 as taught by Heine et al are also performed using ELISA assays. Furthermore, Hitomi et al reference teach an ELISA plate with wells for either a standard substance or specimen, thereby providing the capability of assaying for different samples, including assaying for HNP1-3 as taught by Heine et al.

With regards to claims 87-88, Hitomi et al reference teaches MRP8 as a member of the S100 protein family (i.e. calgranulin A). See column 1, lines 29-30.

With regards to claims 87-88, Hitomi et al reference teaches assay of CAAF1 (i.e. calgranulin C), as stated above. See column 21, line 57.

19. Claims 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Krone et al (Analytical Biochemistry, 1997) as applied to claims 45 and 50 above, and in further view of Heine et al (US 6,174,664 B1).

Hitomi et al and Krone et al references have been disclosed, and Hitomi et al additionally teach an ELISA assay with wells for either a standard substance or specimens. See column 21, lines 62-67. However, Hitomi et al and Krone et al fail to teach that the assay additionally comprises tests for the presence of at least one defensin in said sample of amniotic fluid and that said defensin is HNP-1.

Heine et al teach an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, in order to provide an immunoassay to screen for intra-amniotic infection by detecting a type of neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. See column 1, lines 39-63; column 1, line 66 to column 2, line 9; column 4, lines 25-34; column 6, line 47 to column 7, line 52.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Hitomi et al and Krone et al with an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, as taught Heine et al, in order to provide an immunoassay to screen for intraamniotic infection by detecting a type of

neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. The ability to detect an analyte that is stable and does not degrade provides the motivation to combine the detecting step of Heine et al with the method of Hitomi et al and Krone et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including testing for defensins HNP1-3, as taught by Heine et al, in the method of Hitomi et al and Krone et al, since Hitomi et al and Krone et al teach ELISA assays, and the testing for HNP1-3 as taught by Heine et al are also performed using ELISA assays. Furthermore, Hitomi et al reference teach an ELISA plate with wells for either a standard substance or specimen, thereby providing the capability of assaying for different samples, including assaying for HNP1-3 as taught by Heine et al.

20. Claims 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Burke et al (US 5,965,354).

Hitomi et al reference has been disclosed above, but fails to teach instructions for mixing said adsorbent with a sample of amniotic fluid and monitoring said mixture for binding between said adsorbent and a biomarker in said sample.

Burke et al teach immunoassay instructions, in order to conduct the immunoassay as required. See column 12, lines 37-45.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit of Hitomi et al with immunoassay instructions, as taught by Burke et al, in order to conduct the immunoassay as required. The instructions ensure

that a test is performed correctly, thereby providing motivation to combine the instructions of Burke et al with the kit of Hitomi et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the instructions of Burke et al in the kit of Hitomi et al, since both Hitomi et al and Burke et al teach immunoassays.

With regards to claims 62-63, Hitomi et al reference teaches coating of monoclonal antibodies in an ELISA plate (i.e. antibody immobilized on a solid substrate; enzyme-antibody conjugate used to detect biomarker). See column 21, lines 59-61.

21. Claims 64-67 and 75-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Burke et al (US 5,965,354) as applied to claims 61-61 above, and further in view of Krone et al (Analytical Biochemistry, 1997).

Hitomi et al and Burke et al references have been disclosed above, but fail to teach that the solid substrate is a probe and said biomarker is detected by laser desorption/ionization mass spectrometry.

Krone et al reference teaches a BIAcore CM5 biosensor chip (i.e. probe) that is covalently derivatized with an antibody, and the step wherein species detected during surface plasmon resonance for biomolecular interaction analysis is interfaced with MALDI mass spectrometry (i.e. laser desorption/ionization mass spectrometry; pattern recognition analysis that is keyed to at least one peak), in order to perform ligand identification and quantitation, and allow for the rapid, sensitive, and accurate

investigations of biomolecular interactions. See page 125, right column, 1st full paragraph to page 126, left column, 1st full paragraph; and page 131, right column, 1st full paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit of Hitomi et al and Burke et al with a BIAcore CM5 biosensor chip covalently derivatized with an antibody, and the step wherein species detected during surface plasmon resonance for biomolecular interaction analysis is interfaced with MALDI mass spectrometry, as taught by Krone et al, in order to perform ligand identification and quantitation, and allow for the rapid, sensitive, and accurate investigations of biomolecular interactions. The benefits of quantifiable results, efficiency, and effectiveness provide the motivation to combine the BIAcore BM5 biosensor chip and the MALDI mass spectrometry of Krone et al in the kit of Hitomi et al and Burke et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including a BIAcore CM5 biosensor chip and detection step using MALDI mass spectrometry, as taught by Krone et al, in the kit of Hitomi et al and Burke et al, since Hitomi et al and Burke et al teach binding interactions between antigen and antibody, and the chip and detection method of Krone et al are used to detect antigen binding to immobilized antibody on a chip surface.

With regards to claim 67, Hitomi et al reference teaches anti-CAAF1 monoclonal antibody CAAF1-22-5 (i.e. hydrophobic adsorbent). See column 21, lines 57-58.

With regards to claim 75, Hitomi et al reference teaches MRP8 as a member of the S100 protein family (i.e. calgranulin A). See column 1, lines 29-30.

With regards to claim 76, Hitomi et al reference teaches assay of CAAF1 (i.e. calgranulin C), as stated above. See column 21, line 57.

22. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Burke et al (US 5,965,354) as applied to claims 61-61 above, and further in view of Krone et al (Analytical Biochemistry, 1997) as applied to claim 67, and further in view of Pham (US 2002/0060290).

Hitomi et al, Burke et al, and Krone et al references have been disclosed above, but fail to teach that said probe is a Ciphergen H4 probe.

Pham reference teaches a hydrophobic H4 chip from Ciphergen Biosystems, Inc. in order to provide a substrate with a reverse phase adsorbent for hydrophobic interactions. See page 5, sections 0073-0079.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit of Hitomi et al, Burke et al, and Krone et al with a hydrophobic H4 chip from Ciphergen Biosystems, Inc. as taught by Pham, in order to provide a substrate with a reverse phase adsorbent for hydrophobic interactions. The advantage of having a substrate specific for hydrophobic interactions provides the motivation to combine the hydrophobic H4 chip of Pam with the kit of Hitomi et al, Burke et al, and Krone et al. In addition, one of ordinary skill in the art at the time of the invention would have reasonable expectation of success in including a Ciphergen H4 probe, as taught

by Pham, in the kit of Hitomi et al, Burke et al, and Krone et al, since Hitomi et al, Burke et al, and Krone et al teach a kit with immobilized antibodies on a chip surface, and the Ciphergen H4 probe is one example of a chip with the capability to immobilize adsorbents on a surface to bind analytes.

23. Claims 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Burke et al (US 5,965,354) as applied to claims 61 and 63, and further in view of Heine et al (US 6,174,664 B1).

Hitomi et al and Burke et al references have been disclosed, and Hitomi et al additionally teach an ELISA assay with wells for either a standard substance or specimens. See column 21, lines 62-67. However, Hitomi et al and Burke et al fail to teach that the assay additionally comprises tests for the presence of at least one defensin in said sample of amniotic fluid and that said defensin is HNP-1.

Heine et al teach an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, in order to provide an immunoassay to screen for intraamniotic infection by detecting a type of neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. See column 1, lines 39-63; column 1, line 66 to column 2, line 9; column 4, lines 25-34; column 6, line 47 to column 7, line 52.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Hitomi et al and Burke et al with an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, as taught Heine et al, in order to provide an immunoassay to screen for intraamniotic infection by detecting a type of

neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. The ability to detect an analyte that is stable and does not degrade provides the motivation to combine the detecting step of Heine et al with the method of Hitomi et al and Burke et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including testing for defensins HNP1-3, as taught by Heine et al, in the method of Hitomi et al and Burke et al, since Hitomi et al and Burke et al teach ELISA assays, and the testing for HNP1-3 as taught by Heine et al are also performed using ELISA assays. Furthermore, Hitomi et al reference teach an ELISA plate with wells for either a standard substance or specimen, thereby providing the capability of assaying for different samples, including assaying for HNP1-3 as taught by Heine et al.

24. Claims 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Burke et al (US 5,965,354) as applied to claims 61-61 above, and further in view of Krone et al (Analytical Biochemistry, 1997) as applied to claim 65 above, and further in view of Heine et al (US 6,174,664 B1).

Hitomi et al, Burke et al, and Krone et al references have been disclosed, and Hitomi et al additionally teach an ELISA assay with wells for either a standard substance or specimens. See column 21, lines 62-67. However, Hitomi et al, Burke et al, and Krone et al fail to teach that the assay additionally comprises tests for the presence of at least one defensin in said sample of amniotic fluid and that said defensin is HNP-1.

Heine et al teach an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, in order to provide an immunoassay to screen for intraamniotic infection by detecting a type of neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. See column 1, lines 39-63; column 1, line 66 to column 2, line 9; column 4, lines 25-34; column 6, line 47 to column 7, line 52.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Hitomi et al, Burke et al, and Krone et al with an ELISA in 96-well plates using monoclonal antibodies to defensins HNP1-3, as taught Heine et al, in order to provide an immunoassay to screen for intraamniotic infection by detecting a type of neutrophil defensin that as highly stable and resistant to proteolysis or pH effects. The ability to detect an analyte that is stable and does not degrade provides the motivation to combine the detecting step of Heine et al with the method of Hitomi et al, Burke et al, and Krone et al. In addition, one of ordinary skill in the art at the time of the invention would have had reasonable expectation of success in including testing for defensins HNP1-3, as taught by Heine et al, in the method of Hitomi et al, Burke et al, and Krone et al, since Hitomi et al, Burke et al, and Krone et al teach ELISA assays, and the testing for HNP1-3 as taught by Heine et al are also performed using ELISA assays. Furthermore, Hitomi et al reference teach an ELISA plate with wells for either a standard substance or specimen, thereby providing the capability of assaying for different samples, including assaying for HNP1-3 as taught by Heine et al.

25. Claim 90 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hitomi et al (US 5,976,832) in view of Krone et al (Analytical Biochemistry, 1997). as applied to claim 82 above, and further in view of Parker (US 4,020,006) and Woodruff (US 5,545,616).

Hitomi et al and Krone et al references have been disclosed above, but fail to teach that said patient does not have a white blood cell count that is elevated out of the normal range.

Parker teaches the step of determining the number of white blood cells while performing a procedure, in order to obtain a diagnostic clue on the patient's condition while performing the said procedure. See column 5, lines 19-25.

Woodruff teaches that microbial invasion of the amniotic cavity is evidenced by the presence of an amniotic fluid white blood cell count of greater than 50 cells/mm^3. See column 21, lines 18-34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to include the step of determining the number of white blood cells, as taught by Parker, while performing the calgranulin assay of Hitomi et al and Krone et al, in order to obtain a diagnostic clue on the patient's condition while performing the calgranulin assay. The white blood cell assay of Parker would be able to verify the accuracy of the calgranulin results since both are markers for infection, as taught by Woodruff, thereby providing the motivation to combine the step of Parker with the method of Hitomi et al and Krone et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in performing

the white blood cell assay of Parker with the cells derived from amniotic fluid, as taught by Woodruff, in the method of Hitomi et al and Krone et al, since Hitomi et al and Krone et al teach immunoassays of a biomolecule in amniotic fluid, and the teachings of Parker and Woodruff together disclose an immunoassay of a substance found in amniotic fluid.

Conclusion

26. No claims are allowed.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y Lum whose telephone number is (571) 272-2878. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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